

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
10 April 2003 (10.04.2003)

PCT

(10) International Publication Number  
WO 03/029241 A1(51) International Patent Classification<sup>7</sup>: C07D 333/36, A61K 31/38

(21) International Application Number: PCT/US02/31752

(22) International Filing Date: 4 October 2002 (04.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/326,977 4 October 2001 (04.10.2001) US(71) Applicant (for all designated States except US):  
SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PARRISH, Cynthia, A. [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). CALLAHAN, James, F. [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). LI, Yue [CN/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). STAVENGER, Robert, A. [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). HOLT, Dennis, A. [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US).

(74) Agents: SIMON, Soma, G. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 0939 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/029241 A1

(54) Title: CHK1 KINASE INHIBITORS

(57) Abstract: Novel compounds useful in the inhibition of damage response kinases are provided.

## CHK1 KINASE INHIBITORS

### FIELD OF THE INVENTION

The present invention relates to damage response kinase inhibitors,  
5 especially checkpoint kinase ("chk1 kinase") inhibitors, pharmaceutical compositions comprising these compounds and methods of using these compounds to treat various forms of cancer and hyperproliferative disorders.

### BACKGROUND OF THE INVENTION

The cellular response to DNA damage involves cell cycle delays, increased 10 repair, and apoptosis (Zhou and Elledge *Nature* 2000 408: 433-439). Although many effective cancer therapies work by causing DNA damage induced apoptosis, resistance to these agents remains a significant limitation in the treatment of cancer. One important mechanism of drug resistance is attributed to cell cycle delays (also 15 called checkpoints) and repair activation, which provides both the opportunity and capacity for cells to repair DNA damage. It is likely that approaches abrogating these survival DNA damage responses would have significant clinical utility.

Among different DNA damage response kinases, Chk1 was linked to survival responses including checkpoints. Mice lacking *CHK1* die in early embryogenesis (Liu et al. *Gene & Dev.* 2000 14: 1448-1459; Takai et al. *Gene & Dev.* 2000 14: 1439-1447). ES cells expressing a conditional *CHK1* gene die of p53-independent apoptosis after loss of *CHK1*. Prior to their death, these cells become incapable of preventing mitotic entry in response to IR (Liu et al. *Gene & Dev.* 2000 14: 1448-1459), demonstrating that Chk1 is required for the G2 DNA damage checkpoint in mammals as previously observed in other organisms.

25 Chk1 prevents mitotic entry as follows. Arrest in G2 is regulated by the maintenance of inhibitory phosphorylation of Cdc2 (Nurse *Cell* 1997 91: 865-867). Cdc2 dephosphorylation and activation is catalyzed by the dual specificity phosphatase Cdc25 (Morgan *Nature* 1995 374: 131-134). Recent evidence indicates that part of the G2/M DNA checkpoint mechanism involves inactivation and 30 translocation of Cdc25C into the cytoplasm. This is at least partially mediated by phosphorylation on Ser-216 in Cdc25C and its consequent binding with 14-3-3

proteins (Peng et al. *Science* 1997 277: 1501-1505; Dalal et al. *Mol. Cell Bio.* 1999 19: 4465-4479; Yang et al. *EMBO J.* 1999 18: 2174-2183). Chk1 (Sanchez et al. *Science* 1997 277: 1497-1501) has been shown to phosphorylate Cdc25C at Ser-216 *in vitro*. This modification is thought to maintain Cdc25C phosphorylation in cells 5 arrested at G2/M in response to DNA damage. Recently, staurosporine-like kinase inhibitors, UCN-01 and SB-218078, have been shown to be potent Chk1 inhibitors (Jackson et al. *Cancer Res.* 2000 60: 566-572; Graves et al. *J. Biol. Chem.* 2000 275: 5600-5605). *In vivo*, they can abrogate the G2/M checkpoint induced by DNA damaging agents and enhance the cytotoxicities of the DNA damaging agents. Thus 10 it is likely that a specific Chk1 inhibitor could be used clinically in combination treatment with conventional therapies. Since Chk1 is an essential kinase for regular cell cycle (Liu et al., *Gene & Dev.* 2000 14: 1448-1459), it is possible that Chk1 inhibitors could also be used alone in cancer therapy.

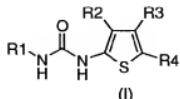
15 Based on the foregoing, there is a need to identify a potent chk1 kinase inhibitors for the treatment of the various aforementioned indications.

### SUMMARY OF THE INVENTION

The present invention involves 2-ureidothiophene compounds represented by 20 Formula (I) hereinbelow, pharmaceutical compositions comprising such compounds and methods of inhibiting chk1 kinase as well as specific assays to detect inhibition of chk1 kinase activity.

### DETAILED DESCRIPTION OF THE INVENTION

25 The present invention provides compounds of Formula (I), hereinbelow:



wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH, C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl, with the preferred substitution being H or CH<sub>3</sub>;

X is selected from the group consisting of O, S, and NH;

5 R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>, C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>5</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>5</sup>R<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-5</sub>aryl, such that any of the foregoing may be optionally substituted by one or more of group A and

10 15 on any position;

R3 is H or halogen, with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position.

A is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COP<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein

20 25 C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>0-5</sub>heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion including, but not limited to, bisulfate, chloride, fumarate, iodide, maleate, methanesulfonate, trifluoromethanesulfonate, nitrate, or sulfate;

D is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl,

5 C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>,

10 S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>3</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>6</sub>heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

15 R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are independently selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>7</sup> and R<sup>8</sup> taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>6</sub>aryl, wherein any of the foregoing may be optionally substituted by one or more of group E and on any position;

E is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl,

25 C(=NH)R<sup>10</sup>, COR<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, CON(O)R<sup>10</sup>R<sup>11</sup>, CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, CO<sub>2</sub>R<sup>10</sup>, C(O)SR<sup>10</sup>, C(S)R<sup>10</sup>, cyano, trifluoromethyl, NR<sup>10</sup>R<sup>11</sup>, N(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>COR<sup>10</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CON(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>CO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>C(O)SR<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, nitro, OR<sup>10</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>10</sup>, S(O)R<sup>10</sup>, S(O)<sub>2</sub>R<sup>10</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>,

30 SO<sub>3</sub>R<sup>10</sup>, PO<sub>3</sub>R<sup>10</sup>R<sup>11</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl

may be optionally substituted by one or more of C(=NH)R<sup>10</sup>, COR<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, CON(O)R<sup>10</sup>R<sup>11</sup>, CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, CO<sub>2</sub>R<sup>10</sup>, C(O)SR<sup>10</sup>, C(S)R<sup>10</sup>, cyano, trifluoromethyl, NR<sup>10</sup>R<sup>11</sup>, N(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>COR<sup>10</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CON(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>CO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>C(O)SR<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>,  
5 nitro, OR<sup>10</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>10</sup>, S(O)R<sup>10</sup>, S(O)<sub>2</sub>R<sup>10</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)CF<sub>3</sub>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>2</sub>R<sup>10</sup>, PO<sub>2</sub>R<sup>10</sup>R<sup>11</sup>, or halo, and on any position;  
R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are independently selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, 10 C<sub>6-6</sub> alkylheterocyclyl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>10</sup> and R<sup>11</sup> taken together with the nitrogen to which they are attached complete a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-4</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl.

This invention also covers pharmaceutically acceptable inorganic or organic salts, esters, and other prodrugs of formula (I).

15 As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined together by single carbon-carbon bonds. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Preferably, the group is saturated linear or cyclic.

20 The term "alkanoyl" is used herein at all occurrences to mean a C(O)alkyl group, wherein the alkyl portion is as defined below, including, but not limited to, acetyl, pivaloyl, and the like.

25 The term "alkenyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one double bond between two of the carbon atoms in the chain, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like.

The term "alkoxy" is used herein at all occurrences to mean a straight or branched chain radical bonded to an oxygen atom, including, but not limited to, methoxy, ethoxy, n- propoxy, isopropoxy, and the like.

30 The term "alkylaryl" is used herein at all occurrences to mean an aryl group as defined below attached to an alkyl group as defined above, including, but not limited to, benzyl and phenethyl, and the like.

The term "alkylheterocyclyl" is used herein at all occurrences to mean a heterocyclic group as defined below attached to an alkyl group as defined above, including, but not limited to, (tetrahydro-3-furanyl)methyl and 3-(4-morpholinyl)propyl, and the like.

5 The term "alkylheteroaryl" is used herein at all occurrences to mean a heteroaryl group as defined below attached to an alkyl group as defined above, including, but not limited to, 3-(furanyl)methyl and (2-pyridinyl)propyl, and the like.

10 The term "alkynyl" is used herein at all occurrences to mean a straight or branched chain radical, wherein there is at least one triple bond between two of the 10 carbon atoms in the chain, including, but not limited to, acetylene, 1-propylene, 2-propylene, and the like.

The term "aralkyl" is used herein at all occurrences to mean an aryl moiety as defined below, which is connected to an alkyl moiety as defined above, including, but not limited to, benzyl or phenethyl, and the like.

15 The term "aryl" is used herein at all occurrences to mean 6-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthalenyl, biphenyl, phenanthryl, anthracenyl, and the like.

20 The term "aryloxy" is used herein at all occurrences to mean an aryl group as defined above linked via an oxy group, including, but not limited to, phenoxy, and the like.

25 The terms "cycloalkyl" is used herein at all occurrences to mean cyclic radicals, which may be mono- or bicyclo- fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

30 The term "heteroaryl" is used herein at all occurrences to mean a 5-14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, which ring or ring systems contain 1 to 4

heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C<sub>1</sub>-alkyl, oxygen, and sulfur, including, but not limited to, indolyl, benzofuranyl, thianaphthetyl, quinolyl, isoquinolyl, pyrrolyl, furanyl, thienyl, pyridyl, and the like.

5 The term "heteroaryloxy" is used herein at all occurrences to mean an heteroaryl group as defined above linked via an oxy group, including, but not limited to, 2-pyridinyloxy, and the like.

10 The term "heterocyclic" is used herein at all occurrences to mean a saturated or wholly or partially unsaturated 5-10-membered ring system (unless the cyclic ring system is otherwise limited) in which one or more rings contain one or more heteroatoms selected from nitrogen, which may be optionally substituted with hydrogen or C<sub>1</sub>-alkyl, oxygen, and sulfur, including, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, pyrazolidine, 1,2,3,6-tetrahydropyridine, hexahydroazepine, and the like.

15 Preferred compounds useful in the present invention include:

- 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide
- 5-Phenyl-2-ureido-thiophene-3-carboxylic acid amide
- 2-(3-Ethyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide
- 5-(3-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide
- 20 5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide
- 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- 5-Phenyl-2-ureido-thiophene-3-carboxylic acid methyl ester
- [5-Phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea
- 2-(3-Methyl-ureido)-5-p-tolyl-thiophene-3-carboxylic acid amide
- 25 5-(2-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide
- 5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide
- [5-(4-Fluoro-phenyl)-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea
- 5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide
- 5-(2-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- 30 5-(4-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide
- 5-p-Tolyl-2-ureido-thiophene-3-carboxylic acid amide
- 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide
- 5-Naphthalen-2-yl-2-ureido-thiophene-3-carboxylic acid amide
- 1-Methyl-3-[5-phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea

SB-715135: 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide  
SB-715515: 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid methylamide  
SB-719113: 5-(3-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719114: 5-(3-Cyano-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5 SB-719116: 5-(4-Ethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719118: 5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719119: 5-(3-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719120: 5-(3-Hydroxymethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719121: 5-(4-Chloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
10 10 SB-719122: 5-(3,4-Dichloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719123: 5-(3-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719124: 5-(4-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-719578: 5-(3-Chloro-4-fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-723730: 5-(4-Methanesulfonyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
15 15 SB-725077: 5-(3,4-Difluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
SB-729585: 5-(4-Cyano-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729586: 5-(4-Dimethylamino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729587: 5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729589: 5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
20 20 SB-729590: 5-(3-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729592: 5-(3-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729593: 5-Benzol[1,3]dioxol-5-yl-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729595: 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-729596: 5-(3-Hydroxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
25 25 SB-733258: 5'-Methyl-5-(3-methyl-ureido)-[2,2]bithiophenyl-4-carboxylic acid amide  
SB-733261: 5-(3-Acetyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
SB-734365: 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid methylamide  
SB-734366: 2-(3-Methyl-ureido)-5-(3-trifluoromethyl-phenyl)-thiophene-3-carboxylic acid  
methylamide  
30 30 SB-734367: 5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
SB-734375: 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
SB-734376: 5-(4-Hydroxy-3-methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid  
methylamide  
SB-734377: 5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid  
35 35 methylamide  
SB-735372: 5-(3,4-Dimethoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
SB-737582: 5-Phenyl-2-ureido-thiophene-3-carboxylic acid phenylamide

**SB-738553:** 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid phenylamide; and  
**SB-738555:** 5-Phenyl-2-ureido-thiophene-3-carboxylic acid methylamide.

More preferred compounds useful in the present invention include:

- 5   **SB-677216:** 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide
- SB-696446:** 5-Phenyl-2-ureido-thiophene-3-carboxylic acid amide
- SB-703954:** 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- SB-710860:** 5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide
- SB-714903:** 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide
- 10   **SB-715135:** 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide
- SB-719113:** 5-(3-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- SB-719116:** 5-(4-Ethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- SB-719118:** 5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- 15   **SB-719120:** 5-(3-Hydroxymethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- SB-723730:** 5-(4-Methanesulfonyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide
- SB-734365:** 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid methylamide
- SB-734366:** 2-(3-Methyl-ureido)-5-(3-trifluoromethyl-phenyl)-thiophene-3-carboxylic acid methylamide
- 20   **SB-734375:** 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide
- SB-734377:** 5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide; and
- SB-735372:** 5-(3,4-Dimethoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Geometric isomers and tautomers of the present compounds are also within the scope of the present invention.

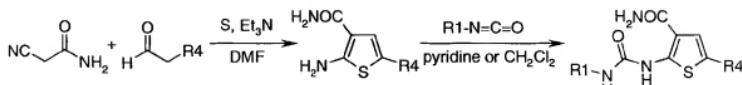
The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

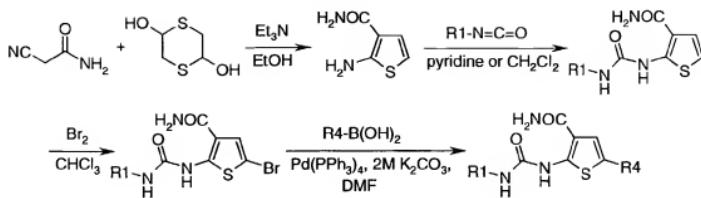
Thiophenes of formula (I) can be prepared using two main methods from known or commercially available starting materials. Following the procedure of U.S. Patent No. 3,963,750, triethylamine is added to a solution of cyanoacetamide and sulfur in *N,N*-dimethylformamide at 40-45 °C and the resulting solution is treated with an aryl acetaldehyde to provide a 2-aminothiophene (Scheme I). Similarly, various alkyl/aryl cyanoacetates, alkyl/aryl sulfonylacetonitriles, and alkyl/aryl cyanoacetamides can be used in place of the cyanoacetamide. Treatment of the 2-aminothiophene with an isocyanate, for example methyl isocyanate or chlorosulfonyl isocyanate, under standard conditions, for example in pyridine or dichloromethane from 23-50 °C, affords the corresponding 2-ureidothiophene.

**Scheme I**



Alternatively, following the method of K. H. Weber and H. Daniel (Liebigs Ann. Chem. 1979, 328-333) cyanoacetamide and mercaptoacetaldehyde in ethanol are treated with triethylamine under reflux to provide the 2-aminothiophene (Scheme II). Treatment of the 2-aminothiophene with an isocyanate, for example methyl 5 isocyanate or chlorosulfonyl isocyanate, under standard conditions, for example in pyridine or dichloromethane from 23-50 °C, gives the 2-ureidothiophene. Bromination of this material, for example with bromine in chloroform at room temperature, then affords the 5-bromo-2-ureidothiophene, which can be treated with various aryl or heteroaryl boronic acids (or acid equivalents) under standard Suzuki 10 conditions to provide the corresponding 5-aryl/heteroaryl-2-ureidothiophene analogs.

Scheme II



5 The following examples further illustrate the synthesis of the present compounds but  
are not intended to be limiting in any way:

**Example 1**

Preparation of 5-(4-fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid  
10 amide and 5-(4-fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

a) 2-Amino-5-(4-fluorophenyl)-3-thiophene carboxamide

As described in U.S. Patent No. 3,963,750 (A. C. Goudie), a stirred mixture  
of cyanoacetamide (0.1 mol), sulfur (0.1 mol), and *N,N*-dimethylformamide (20 mL)  
15 at 40-45 °C was treated with triethylamine (7.5 mL). The resulting solution was  
treated dropwise over 1.5 h with 4-fluorophenylacetaldehyde (0.1 mol, prepared by  
oxidation of 4-fluorophenethyl alcohol with pyridinium chlorochromate (1.5 equiv)  
in dichloromethane) while the reaction mixture was maintained at 40-45 °C. After  
the solution was stirred at room temperature for 16 h, it was cooled (ice bath) and  
20 poured onto water (60 mL) at 5 °C. The precipitate was collected by filtration,  
washed with water and dried. Recrystallization from propanol gave the above title  
compound (40%, m.p. 227-230 °C).

## b) 5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

To a room temperature solution of 2-amino-5-(4-fluorophenyl)-3-thiophene carboxamide (0.6 mmol) in pyridine (5 mL) was added methyl isocyanate (1.9 mmol). The reaction mixture was stirred overnight and then diluted with methanol and concentrated in vacuo. Upon addition of methanol, the product was precipitated and collected via filtration. ESIMS [M+H]<sup>+</sup>: 294.

## c) 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

To a room temperature solution of 2-amino-5-(4-fluorophenyl)-3-thiophene carboxamide (4.2 mmol) in dichloromethane (22 mL) was added chlorosulfonyl isocyanate (4.2 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with the addition of water. The crude mixture was filtered, concentrated in vacuo, and then dissolved in DMSO. Purification by Gilson reverse phase HPLC provided the title product. ESIMS [M+H]<sup>+</sup>: 280.

15

**Example 2**

Preparation of 2-(3-methyl-ureido)-5-p-tolyl-thiophene-3-carboxylic acid amide and 5-p-tolyl-2-ureido-thiophene-3-carboxylic acid amide

## 20 a) 2-Amino-5-p-tolyl-3-thiophene carboxamide

Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with p-tolylacetaldehyde provided the title compound (m.p. 228-230 °C).

## 25 b) 2-(3-Methyl-ureido)-5-p-tolyl-thiophene-3-carboxylic acid amide

To a room temperature solution of 2-amino-5-p-tolyl-3-thiophene carboxamide (0.13 mmol) in pyridine (1.0 mL) was added methyl isocyanate (0.42 mmol). The reaction mixture was stirred overnight and then diluted with methanol and concentrated in vacuo. Upon addition of methanol, the product was precipitated and collected via filtration (71%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.66 (br s, 2H),

7.66 (s, 1H), 7.40 (d, 2H,  $J$  = 8.1 Hz), 7.32 (br s, 1H), 7.21 (d, 2H,  $J$  = 8.0 Hz), 2.66 (d, 3H,  $J$  = 4.5 Hz), 2.30 (s, 3H).

c) 5-p-Tolyl-2-ureido-thiophene-3-carboxylic acid amide

5 To a room temperature solution of 2-amino-5-p-tolyl-3-thiophene carboxamide (0.13 mmol) in dichloromethane (1.0 mL) was added chlorosulfonyl isocyanate (0.14 mmol). The reaction mixture was stirred for 4 h, quenched with the addition of water (0.5 mL), and then stirred overnight. After concentrating in vacuo, the reaction mixture was dissolved in DMSO and purified by Gilson reverse phase

10 HPLC to afford the title product. ESIMS [M+H] $^+$ : 276.0.

#### Example 3

Preparation of 5-(4-chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

15 a) 2-Amino-5-(4-chlorophenyl)-3-thiophene carboxamide  
Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with 4-chlorophenylacetaldehyde provided the title compound (m.p. 255-257 °C).

20 b) 5-(4-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
To a room temperature solution of 2-amino-5-(4-chlorophenyl)-3-thiophene carboxamide (0.13 mmol) in pyridine (1.0 mL) was added methyl isocyanate (0.42 mmol). The reaction mixture was stirred overnight and then diluted with methanol

25 and concentrated in vacuo. The reaction mixture was dissolved in DMSO and purified by Gilson reverse phase HPLC to provide the title compound. ESIMS [M+H] $^+$ : 310.2.

#### Example 4

30 Preparation of 5-(3-chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

## a) 2-Amino-5-(3-chlorophenyl)-3-thiophene carboxamide

Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with 3-chlorophenylacetaldehyde provided the title compound (m.p. 190-192 °C).

## b) 5-(3-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 3(b) with 2-amino-5-(3-chlorophenyl)-3-thiophene carboxamide provided the title compound. ESIMS 10 [M+H]<sup>+</sup>: 310.

**Example 5**

Preparation of 2-(3-methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide and 5-phenyl-2-ureido-thiophene-3-carboxylic acid amide

15 a) 2-Amino-5-phenyl-3-thiophene carboxamide

Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with phenylacetaldehyde provided the title compound.

20 b) 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide

Following the procedure described in Example 3(b) with 2-amino-5-phenyl-3-thiophene carboxamide provided the title compound. ESIMS [M+H]<sup>+</sup>: 276.

## c) 5-Phenyl-2-ureido-thiophene-3-carboxylic acid amide

25 Following the procedure described in Example 2(c) with 2-amino-5-phenyl-3-thiophene carboxamide afforded the title compound. ESIMS [M+H]<sup>+</sup>: 262.

**Example 6**

Preparation of 2-(3-ethyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide

30 a) 2-(3-Ethyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide

Using the product of Example 5(a) and following the procedure described in Example 3(b) but replacing methyl isocyanate with ethyl isocyanate gave the title compound. ESIMS  $[M+H]^+$ : 290.

5

### Example 7

Preparation of 5-phenyl-2-ureido-thiophene-3-carboxylic acid methyl ester

a) 2-Amino-5-phenyl-thiophene-3-carboxylic acid methyl ester

Using the procedure described in Example 1(a) but replacing cyanoacetamide with methyl cyanoacetate and 4-fluorophenylacetaldehyde with phenylacetaldehyde gave the title product.

b) 5-Phenyl-2-ureido-thiophene-3-carboxylic acid methyl ester

Following the procedure described in Example 2(c) with 2-amino-5-phenyl-thiophene-3-carboxylic acid methyl ester afforded the title compound. ESIMS  $[M+H]^+$ : 277.

### Example 8

Preparation of 5-(4-fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide and 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide

a) 2-Amino-5-(4-fluoro-phenyl)-thiophene-3-carboxylic acid methylamide

Using the procedure described in Example 1(a) but replacing cyanoacetamide with methyl cyanoacetamide provided the title product.

b) 5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 3(b) with 2-amino-5-(4-fluoro-phenyl)-thiophene-3-carboxylic acid methylamide provided the title compound (65%).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.18 (br s, 1H), 7.73 (br s, 1H),

7.65 (s, 1H), 7.53 (m, 2H), 7.26 (t, 2H,  $J$  = 8.8 Hz), 2.79 (d, 3H,  $J$  = 4.4 Hz), 2.67 (d, 3H,  $J$  = 4.3 Hz). ESIMS [M+H]<sup>+</sup>: 308.2.

c) 5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide  
5 Following the procedure described in Example 2(c) with 2-amino-5-(4-fluoro-phenyl)-thiophene-3-carboxylic acid methylamide gave the title compound. ESIMS [M+H]<sup>+</sup>: 294.0.

**Example 9**

Preparation of 2-(3-methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid methylamide and 5-phenyl-2-ureido-thiophene-3-carboxylic acid methylamide

5 a) 2-Amino-5-phenyl-thiophene-3-carboxylic acid methylamide

Using the procedure described in Example 5(a) but replacing cyanoacetamide with methyl cyanoacetamide provided the title product.

b) 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid methylamide

10 Following the procedure described in Example 3(b) with 2-amino-5-phenyl-thiophene-3-carboxylic acid methylamide provided the title compound.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.20 (br s, 1H), 7.71 (s, 2H), 7.51 (d, 2H,  $J$  = 7.2 Hz), 7.40 (t, 2H,  $J$  = 7.7 Hz), 7.25 (t, 1H,  $J$  = 7.4 Hz), 2.79 (d, 3H,  $J$  = 4.5 Hz), 2.68 (d, 3H,  $J$  = 4.3 Hz). ESIMS  $[\text{M}+\text{H}]^+$ : 290.2.

15

c) 5-Phenyl-2-ureido-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 2(c) with 2-amino-5-phenyl-thiophene-3-carboxylic acid methylamide provided the title compound. ESIMS  $[\text{M}+\text{H}]^+$ : 276.0.

20

**Example 10**

Preparation of 5-Naphthalen-2-yl-2-ureido-thiophene-3-carboxylic acid amide

a) 2-Amino-5-naphthalen-2-yl-thiophene-3-carboxylic acid amide

25 Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with naphthalene-2-carbaldehyde provided the title compound.

b) 5-Naphthalen-2-yl-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 2(c) with 2-amino-5-naphthalen-2-yl-thiophene-3-carboxylic acid amide afforded the title compound. ESIMS  $[M+H]^+$ : 312.

5

### Example 11

Preparation of 5-(2-fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide and 5-(2-fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

a) 2-Amino-5-(2-fluoro-phenyl)-3-thiophene carboxamide

10 Using the procedure described in Example 1(a) but replacing 4-fluorophenylacetaldehyde with 2-fluorophenylacetaldehyde provided the title compound (62%). ESIMS  $[M+H]^+$ : 294.2.

b) 5-(2-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

15 Following the procedure described in Example 2(c) with 2-amino-5-(2-fluoro-phenyl)-3-thiophene carboxamide afforded the title compound. ESIMS  $[M+H]^+$ : 280.0.

c) 5-(2-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

20 Following the procedure described in Example 3(b) with 2-amino-5-(2-fluoro-phenyl)-3-thiophene carboxamide afforded the title compound. ESIMS  $[M+H]^+$ : 294.2.

### Example 12

25 Preparation of 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid phenylamide and 5-Phenyl-2-ureido-thiophene-3-carboxylic acid phenylamide

a) 2-Amino-5-phenyl-thiophene-3-carboxylic acid phenylamide

Using the procedure described in Example 5(a) but replacing cyanoacetamide with phenyl cyanoacetamide provided the title product.

## b) 2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid phenylamide

Following the procedure described in Example 3(b) with 2-amino-5-phenyl-thiophene-3-carboxylic acid phenylamide at 50 °C overnight provided the title compound. ESIMS [M+H]<sup>+</sup>: 352.2.

5

## c) 5-Phenyl-2-ureido-thiophene-3-carboxylic acid phenylamide

Following the procedure of Example 2(c) with 2-amino-5-phenyl-thiophene-3-carboxylic acid phenylamide provided the title compound. ESIMS [M+H]<sup>+</sup>: 338.2.

10

**Example 13**

## Alternative Preparation of 2-Ureidothiophenes (Scheme II)

## a) 2-Amino-3-thiophene carboxamide

15 Triethylamine (127 mmol) was added to a suspension of 1,4-dithiane-2,5-diol (64 mmol) and 2-cyanoacetamide (64 mmol) in ethanol. The reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled and filtered, and the filtrate was concentrated in vacuo. The crude mixture was dissolved in ethyl acetate (300 mL) and washed with 2.5N aqueous sodium hydroxide solution (2 x 100 mL) 20 and brine (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to afford the title compound (86%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.21 (br s, 3H), 7.04 (d, 1H, *J* = 5.8 Hz), 6.73 (br s, 1H), 6.22 (d, 1H, *J* = 5.8 Hz).

25 b) 2-(3-Methyl-ureido)-3-thiophene carboxamide

To a room temperature solution of 2-amino-3-thiophene carboxamide (35 mmol) in pyridine (100 mL) was added methyl isocyanate (106 mmol). The reaction mixture was stirred overnight and then diluted with methanol (100 mL) and concentrated in vacuo. The crude mixture was purified by flash chromatography 30 (10% methanol/dichloromethane) to yield the title compound (79%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.17 (d, 1H, *J* = 5.9 Hz), 6.68 (d, 1H, *J* = 5.9 Hz), 2.79 (s, 3H).

## c) 2-Ureido-3- thiophene carboxamide

5 To a room temperature solution of 2-amino-3-thiophene carboxamide (7 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) was added chlorosulfonyl isocyanate (14 mmol). A white precipitate formed as the reaction mixture stirred overnight. The reaction was quenched with  $\text{H}_2\text{O}$  (20 mL) and stirred for 1 h, then filtered and azeotroped with toluene. The crude residue was used directly in the next reaction. ESIMS  $[\text{M}+\text{H}]^+$ : 186.0.

## 10 d) 5-Bromo-2-(3-methyl-ureido)-3-thiophene carboxamide

Bromine (25 mmol) was added to a room temperature suspension of 2-(3-methyl-ureido)-3-thiophene carboxamide (20 mmol) in chloroform (200 mL). After stirring overnight, the reaction mixture was diluted with methanol and concentrated in vacuo. The crude mixture was purified by flash chromatography (50% ethyl acetate/hexanes) to give the title compound (92%).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.24 (s, 1H), 2.78 (s, 3H).

## e) 5-Bromo-2-ureido-3-thiophene-carboxamide

20 Bromine (2.1 mmol) was added to a room temperature suspension of 2-ureido-3- thiophene carboxamide (1.6 mmol) in chloroform (50 mL). After stirring overnight, the reaction mixture was diluted with methanol and concentrated in vacuo. The crude mixture was purified by flash chromatography (100% ethyl acetate) to give the title compound (94%). ESIMS  $[\text{M}+\text{H}]^+$ : 263.8.

25

Example 14

Preparation of 5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide and 5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

## 30 a) 5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

A solution of 4-methoxyphenyl boronic acid (0.63 mmol) in 1:1 DMF:2M aqueous  $K_2CO_3$  solution (1.0 mL) was added to the 5-bromo-2-(3-methyl-ureido)-3-thiophene carboxamide (0.42 mmol). Catalytic  $(PPh_3)_4Pd$  (5 mol%) was added as well as additional 1:1 DMF:2M aqueous  $K_2CO_3$  solution (1.0 mL). The reaction mixture was heated at 100 °C for 24 h and then cooled. The crude mixture was concentrated in vacuo, dissolved in DMSO, filtered, and purified by Gilson reverse phase HPLC to afford the title product. ESIMS  $[M+H]^+$ : 306.2.

b) 5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

10 A solution of 4-methoxyphenyl boronic acid (0.26 mmol) in 1:1 DMF:2M aqueous  $K_2CO_3$  solution (1.0 mL) was added to 5-bromo-2-ureido-3-thiophene-carboxamide (0.13 mmol). Catalytic  $(PPh_3)_4Pd$  (5 mol%) was added as well as additional 1:1 DMF:2M aqueous  $K_2CO_3$  solution (1.0 mL). The reaction mixture was heated at 100 °C for 24 h and then cooled. The crude mixture was concentrated 15 in vacuo, dissolved in DMSO, filtered, and purified by Gilson reverse phase HPLC to afford the title product. ESIMS  $[M+H]^+$ : 292.2.

**Example 15**

Preparation of 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide and 20 5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide

a) 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide

Following the procedure described in Example 14(a) with 3-thiopheneboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 282.0.

25

b) 5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide

Following the procedure described in Example 14(b) with 3-thiopheneboronic acid provided the title compound.  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  7.56 (s, 1H), 7.53 (m, 1H), 7.40 (m, 1H), 7.38 (s, 1H).

30

**Example 16**

Preparation of 5-(4-Cyano-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 4-cyanophenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 301.2.

5

**Example 17**

Preparation of 5-(4-Dimethylamino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 4-dimethylamino-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 319.2.

10

**Example 18**

Preparation of 5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

15 Following the procedure described in Example 14(a) with 4-hydroxymethyl-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 306.0.

20

**Example 19**

Preparation of 5-(3-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 3-fluorophenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 294.0.

25

**Example 20**

Preparation of 5-(3-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 3-aminophenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 291.0.

30

**Example 21**

Preparation of 5-Benzo[1,3]dioxol-5-yl-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 3,4-(methylenedioxy)phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 5 320.2.

**Example 22**

Preparation of 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

10 Following the procedure described in Example 14(a) with 4-aminophenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 291.2.

**Example 23**

15 Preparation of 5-(3-Hydroxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 3-hydroxyphenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 292.2.

**Example 24**

20 Preparation of 5'-Methyl-5-(3-methyl-ureido)-[2,2']bithiophenyl-4-carboxylic acid amide

Following the procedure described in Example 14(a) with 5-methyl-2-thiopheneboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 296.2.

25 **Example 25**

Preparation of 5-(3-Acetyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

Following the procedure described in Example 14(a) with 3-acetylphenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 318.2.

30

**Example 26**

Preparation of 5-(3-Methyl-ureido)-[2,3']bithiophenyl-4-carboxylic acid methylamide

a) 2-Amino-thiophene-3-carboxylic acid methylamide

5        Using the procedure described in Example 13(a) but replacing 2-cyanoacetamide with 2-cyanomethylamide provided the title product. ESIMS  $[M+H]^+$ : 157.0.

b) 2-(3-Methyl-ureido)-thiophene-3-carboxylic acid methylamide

10      Using the procedure described in Example 13(b) with the 2-amino-thiophene-3-carboxylic acid methylamide gave the title product. ESIMS  $[M+H]^+$ : 214.0.

c) 5-Bromo-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

15      Using the procedure described in Example 13(d) with the 2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide gave the title product. ESIMS  $[M+H]^+$ : 292.0.

d) 5-(3-Methyl-ureido)-[2,3']bithiophenyl-4-carboxylic acid methylamide

20      Following the procedure described in Example 14(a) with 3-thiopheneboronic acid and 5-bromo-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide provided the title compound. ESIMS  $[M+H]^+$ : 296.0.

Example 27

25      Preparation of 2-(3-Methyl-ureido)-5-(3-trifluoromethyl-phenyl)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 3-trifluoromethyl-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 358.0.

Preparation of 5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 4-methoxy-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 320.2.

5

**Example 29**

Preparation of 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 4-amino-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 303.0.

10

**Example 30**

Preparation of 5-(4-Hydroxy-3-methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 4-hydroxy-3-methoxy-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 336.2.

15

**Example 31**

Preparation of 5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 4-hydroxymethyl-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 319.8.

20

**Example 32**

Preparation of 5-(3,4-Dimethoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide

Following the procedure described in Example 26(d) with 3,4-dimethoxy-phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 350.2.

30

**Example 33**

Preparation of 5-(3-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

To a 5 mL reaction vial was added sequentially 5-bromo-2-ureido-3-thiophene-carboxamide (0.25 mmol), potassium acetate (0.50 mmol), tetrakis(triphenylphosphine)palladium(0) (5 mol%), 3-fluoro-phenylboronic acid (0.275 mmol), absolute ethanol (2.0 mL), and toluene (2.0 mL). The reaction vial 5 was sealed and heated to 90-95 °C for 12 h. The solvent was removed in vacuo, and the residue was dissolved in dimethylsulfoxide, filtered, and purified by Gilson reverse phase HPLC to provide the title compound. ESIMS [M+H]<sup>+</sup>: 280.

#### Example 34

10 Preparation of 5-(3-Cyano-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3-cyano-phenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 287.

#### Example 35

15 Preparation of 5-(4-Ethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 4-ethyl-phenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 290.

#### Example 36

20 Preparation of 5-(3-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3-methoxy-phenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 292.

#### Example 37

25 Preparation of 5-(3-Hydroxymethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3-hydroxymethyl-phenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 292.

30

#### Example 38

Preparation of 5-(4-Chloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 4-chlorophenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 296.

**Example 39**

5 Preparation of 5-(3,4-Dichloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3,4-dichlorophenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 331.

**Example 40**

10 Preparation of 5-(3-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3-trifluoromethylphenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 330.

15

**Example 41**

Preparation of 5-(4-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 4-trifluoromethylphenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 330.

20

**Example 42**

Preparation of 5-(3-Chloro-4-fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

25 Following the procedure described in Example 33 with 3-chloro-4-fluorophenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 314.

**Example 43**

Preparation of 5-(4-Methanesulfonyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

30 Following the procedure described in Example 33 with 4-methanesulfonylphenylboronic acid provided the title compound. ESIMS [M+H]<sup>+</sup>: 340.

**Example 44**

Preparation of 5-(3,4-Difluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide

Following the procedure described in Example 33 with 3,4-difluoro-  
5 phenylboronic acid provided the title compound. ESIMS  $[M+H]^+$ : 298.

**Example 45**

Preparation of [5-Phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea and 1-methyl-  
3-[5-phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea

10

a) [1-(2-Amino-5-phenyl-thiophen-3-yl)-methanoyl]-urea

Using the procedure described in Example 1(a) but replacing cyanoacetamide with (2-cyano-ethanoyl)-urea provided the title product upon Gilson reverse phase HPLC purification (53%). ESIMS  $[M+H]^+$ : 262.

15

b) [5-Phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea

Following the procedure described in Example 2(c) with [1-(2-amino-5-phenyl-thiophen-3-yl)-methanoyl]-urea provided the title compound (74%). ESIMS  $[M+H]^+$ : 305.

20

c) 1-Methyl-3-[5-phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea

Following the procedure described in Example 12(b) with [1-(2-amino-5-phenyl-thiophen-3-yl)-methanoyl]-urea provided the title compound. ESIMS  $[M+H]^+$ : 319.2.

25

**Example 46**

Preparation of [5-(4-Fluoro-phenyl)-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea

Chlorosulfonyl isocyanate (14 mmol) was added dropwise over 10 min to an ice-cooled solution of 2-amino-5-(4-fluoro-phenyl)-thiophene-3-carboxylic acid amide (4.2 mmol) in dichloromethane (22 mL). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture

was quenched with the addition of water (10 mL) and was stirred for an additional 10 min. The reaction mixture was then filtered and the light orange solid was washed with water (2 x 10 mL) and dried to provide the title compound (73%).  
ESIMS [M+H]<sup>+</sup>: 323.

5

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above.

In order to use a compound of Formula (I) or a pharmaceutically acceptable 10 salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Formulations for pharmaceutical use incorporating compounds of the present 15 invention can be prepared in various forms and with numerous excipients.  
Examples of such formulations are given below:

The present ligands can be administered by different routes including 20 intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., 25 intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. 30 For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in

the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

5 For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art. The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC<sub>50</sub>, EC<sub>50</sub>, the biological half-life of the compound, the age, size and weight of the patient, and the 10 disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

15 Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single 20 dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes 25 contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

30 As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease. As used herein, "diseases"

treatable using the present compounds include, but are not limited to leukemias, solid tumor cancers and metastases, lymphomas, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer, head cancer and neck cancer, chronic inflammatory proliferative diseases such as psoriasis and rheumatoid arthritis; proliferative cardiovascular diseases such as restenosis; proliferative ocular disorders such as diabetic retinopathy; and benign hyperproliferative diseases such as hemangiomas.

10        Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

25        Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

30        Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

5 A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

10 Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the tests indicated hereinbelow.

15 **Chk1 Kinase Assay:**

Compounds capable of inhibiting Chk1 kinase can be identified with in vitro assays and cellular assays as described below. Variations of these assays would be obvious to those skilled in the art.

20 Streptavidin coated SPA beads, ATP and  $^{33}\text{P}$ -ATP were obtained from Amersham Pharmacia Biotech, Biotin labeled peptide KVSRSGLYRSPSMPENLNRK(Biotin-xx)NH<sub>2</sub> was obtained from Affiniti Research Products Ltd, assay buffer reagents were obtained from Sigma-Aldrich Co.Ltd. fff84 well assay plates were obtained from Corning Inc. Assay buffer: 50 mM HEPES, 50 mM KCl, 5% Glycerol, 1 mM EGTA, 0.001% Tween-20; 25 enzyme/peptide mix: 25 nM Chk1, 2.5 $\mu\text{M}$  biotin peptide, 7.5 mM 2-mercaptoethanol in assay buffer; ATP mix: 20 $\mu\text{M}$  ATP at 650kBq/mL, 5mM MgCl<sub>2</sub> in assay buffer.

25 Inhibitors of decreasing concentration, from 10 $\mu\text{M}$  were incubated at room temperature for 1 hour together with 5 $\mu\text{L}$  enzyme/peptide mix and 5 $\mu\text{L}$  ATP mix. 30 The reaction was stopped with 5 $\mu\text{L}$  of 0.5M EDTA followed by a further addition of 65 $\mu\text{L}$  of 0.2mg/mL SPA beads. Plates were spun at 2500 rpm for 10 minutes and the

amount of  $^{32}\text{P}$  incorporated onto the peptide was quantified by a Wallac Trilux scintillation counter at a read time of 1 minute per well. IC50's were fitted to the data using SDM Explorer version 2.5 software (©GlaxoSmithKline Plc.).

5 **Expression of GST-Chk1:**

A GST-Chk1 expression construct was constructed which has the glutathione-S-transferase gene fused to the amino terminus of Chk1 kinase via a linker containing a thrombin cleavage site. This construct was cloned into the Baculovirus expression vector, pFASTBAC, and this was used to make the viral 10 stock for the subsequent infection. Spodoptera frugiperda cells (Sf9) were infected with the virus expressing the GST-Chk1 and the cells were grown for 3 days, then harvested and frozen down.

**Purification of GST-Chk1:**

15 The GST-Chk1 protein was purified as follows: An Sf9 cell pellet expressing GST-Chk1 was resuspended on ice in lysis buffer (50mM Tris-Cl, pH 7.5, 250mM NaCl<sub>2</sub>, 1mM dithiothreitol (DTT), 0.1% Brij, 5% (v/v) protease inhibitor cocktail, 1mM sodium orthovanadate), cells were lysed by sonication and centrifuged at 100,000xg for 30min. The supernatant was added to Glutathione Sepharose 4B, 20 beads, equilibrated in wash buffer (20mM Tris-Cl, pH 7.0, 10mM MgCl<sub>2</sub>, 100mM NaCl<sub>2</sub>, 1mM DTT, 0.5% (v/v) protease inhibitor cocktail, 1mM sodium orthovanadate). The mixture was rocked for 30min. The resin with the bound GST-Chk1 was spun down at 500xg for 5min and washed with 14mls of wash buffer. The beads were spun as above and resuspended in another 14mls of wash buffer. 25 The suspension was transferred into a column and allowed to pack, then the wash buffer was allowed to flow through by gravity. The GST-Chk1 was eluted from the column with 10mM Glutathione in 50mM Tris-Cl, pH 8.0 in 500ul fractions. Protein concentrations were determined on the fractions using Bio-Rad's Protein assay kit as per instructions. Fractions containing the GST-Chk1 were pooled and 30 diluted to a concentration of ~0.5mg/ml and dialyzed for 4 hours at 4°C in dialysis buffer (20mM HEPES, pH 7.0, 1mM Manganese Acetate, 100mM NaCl<sub>2</sub>, 0.05%

Brij-35, 10% glycerol, 1mM DTT, 0.2% (v/v) protease inhibitor cocktail, 1mM sodium orthovanadate). The protein was aliquoted and stored at -80°.

**Cell Cycle Studies:**

5 Drug studies considering cellular effects were performed in the Hela S3 adherent cell line. Cells were plated at a concentration sufficiently low such that 24 hours later they were at 10-20% confluence (typically 2x10<sup>5</sup> cells/15cm e3). Cells were then synchronized in S phase by a repeated thymidine block. Briefly, cells were treated with 2mM thymidine for 18hours, released for 8 hours by 3 washes, and then 10 treated again with thymidine. Following the second release from thymidine, 95% of cells were in S phase. Synchronized cells were then returned to complete media containing a DNA-damaging drug such as 50nM topotecan (a dosage we have found to be sufficient to arrest cells in early G2 phase without inducing apoptosis) alone and in combination with test compounds for up to 18 hours. Cell cycle profiles were 15 then performed cytometrically using a procedure for propidium iodide staining of nuclei. (Vindelov et al, Cytometry Vol.3, No.5, 1983, 323-327) CHK1 inhibitors would be expected to reverse the G2 arrest caused by the DNA damaging agent. Typical concentration ranges for such activity would be 0.001 to 10 uM.

**Proliferation/Apoptosis Studies:**

20 Proliferation studies were performed in a variety of adherent and non-adherent cell lines including Hela S3, HT29, and Jurkat. The proliferation assay utilized a colorimetric change resulting from reduction of the tetrazolium reagent XTT into a formazan product by metabolically active cells (Scudiero et al. Cancer Research, 48, 1981, 4827-4833) Cells were seeded in 100ul 25 in 96 well plates to roughly 10% confluence (cell concentration varied with cell lines) and grown for 24 hours. Compounds were then added with or without sufficient vehicle- containing media to raise the cells to a 200ul final volume containing chemical reagents in 0.2% DMSO. Cells received multiple concentrations of DNA-damaging anti-proliferative drugs such as topotecan, test compounds, and 30 combination treatment at 37°C 5% CO<sub>2</sub>. 72 hours later, 50 uls of an XTT/ phenazine methosulfate mixture were added to each well and cells were left to incubate for

90mins. Plate was read at 450nm, and anti-proliferative effects were compared relative to vehicle treated cells. CHK1 inhibitors are expected to enhance the cytotoxicity of DNA-damaging chemotherapeutic drugs. Typical concentration ranges for such activity would be 0.001 to 10 uM. Other assays for cellular 5 proliferation or cytotoxicity could also be used with test compounds, and these assays are known to those skilled in the art.

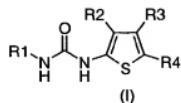
#### **IkB-β Kinase Assay**

IKK-β was expressed as a GST-tagged protein, and its activity was assessed 10 in a 96-well scintillation proximity assay (SPA). Briefly, IKK-β was diluted in assay buffer (20 mM Hepes, pH 7.7, 2 mM MgCl<sub>2</sub>, 1 mM MnCl<sub>2</sub>, 10 mM β-glycerophosphate, 10 mM NaF, 10 mM PNPP, 0.3 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM benzamidine, 2 μM PMSF, 10 μg/ml aprotinin, 1 ug/mL leupeptin, 1 ug/mL pepstatin, 1mM DTT; 20 nM final), with various concentrations of compound or 15 DMSO vehicle, 240 nM ATP and 200 nCi [<sup>32</sup>P]-ATP (10 mCi/mL, 2000 Ci/mmol; NEN Life Science Products, Boston, MA). The reaction was started with the addition of a biotinylated peptide comprising amino acids 15 – 46 of IκB-α (American Peptide) to a final concentration of 2.4 μM, in a total volume of 50 uL. The sample incubated for one hour at 30 °C, followed by the addition of 150 uL of 20 stop buffer (PBS w/o Ca<sup>2+</sup>, Mg<sup>2+</sup>, 0.1% Triton X-100 (v/v), 10 mM EDTA) containing 0.2 mg streptavidin-coated SPA PVT beads (Amersham Pharmacia Biotech, Piscataway, NJ). The sample was mixed, incubated for 10 min. at room temperature, centrifuged (1000 xg, 2 minutes), and measured on a Hewlett-Packard TopCount.

25 All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A method of inhibiting angiogenesis or damage response kinase activity which comprises administering to a subject in need thereof, an effective amount of a 5 compound according to Formula (I) hereinbelow:



wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH, C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl;

10 X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>, C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>5</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>3</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>5</sup>R<sup>6</sup>;

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached, may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, such that

15 any of the foregoing may be optionally substituted by one or more of group A and on any position;

R3 is H or halogen;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position;

20 A is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>,

NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>6-6</sub>heteroaryl, aryloxy, and

5 heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl,

10 C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>COR<sup>7</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein

15 C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>6-6</sub>heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

R<sup>7</sup>, R<sup>8</sup>, and R<sup>9</sup> are independently selected from the group consisting of hydrogen, C<sub>1-10</sub>

20 alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>7</sup> and R<sup>8</sup> taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub>alkyl or (CH<sub>2</sub>)<sub>6-6</sub>aryl, wherein any

25 of the foregoing may be substituted by one or more of group E and on any position;

E is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocyclyl, C<sub>6-6</sub> alkylheteroaryl, C(=NH)R<sup>10</sup>, COR<sup>10</sup>, CONR<sup>10</sup>R<sup>11</sup>, CON(O)R<sup>10</sup>R<sup>11</sup>, CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, CO<sub>2</sub>R<sup>10</sup>, C(O)SR<sup>10</sup>, C(S)R<sup>10</sup>, cyano, trifluoromethyl, NR<sup>10</sup>R<sup>11</sup>, N(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>COR<sup>10</sup>,

30 NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CON(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>CO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>C(O)SR<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, nitro, OR<sup>10</sup>, OCF<sub>3</sub>, aryloxy,

heteroaryloxy,  $\text{SR}^{10}$ ,  $\text{S(O)R}^{10}$ ,  $\text{S(O)}_2\text{R}^{10}$ ,  $\text{SCF}_3$ ,  $\text{S(O)CF}_3$ ,  $\text{S(O)}_2\text{CF}_3$ ,  $\text{SO}_2\text{NR}^{10}\text{R}^{11}$ ,  $\text{SO}_3\text{R}^{10}$ ,  $\text{PO}_3\text{R}^{10}\text{R}^{11}$ , and halo, wherein  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkanoyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-10}$  cycloalkyl,  $\text{C}_{0-6}$  alkylaryl,  $\text{C}_{0-6}$  alkylheterocyclyl,  $\text{C}_{0-6}$  alkylheteroaryl may be substituted by one or more of  $\text{C}(\text{=NH})\text{R}^{10}$ ,  $\text{COR}^{10}$ ,  $\text{CONR}^{10}\text{R}^{11}$ ,

5  $\text{CON(O)R}^{10}\text{R}^{11}$ ,  $\text{CONCR}^{10}\text{R}^{11}\text{R}^{12}\text{Y}$ ,  $\text{CO}_2\text{R}^{10}$ ,  $\text{C(O)SR}^{10}$ ,  $\text{C(S)R}^{10}$ , cyano, trifluoromethyl,  $\text{NR}^{10}\text{R}^{11}$ ,  $\text{N(O)R}^{10}\text{R}^{11}$ ,  $\text{NR}^{10}\text{R}^{11}\text{R}^{12}\text{Y}$ ,  $\text{NR}^{10}\text{COR}^{10}$ ,  $\text{NR}^{10}\text{CONR}^{10}\text{R}^{11}$ ,  $\text{NR}^{10}\text{CON(O)R}^{10}\text{R}^{11}$ ,  $\text{NR}^{10}\text{CONR}^{10}\text{R}^{11}\text{R}^{12}\text{Y}$ ,  $\text{NR}^{10}\text{CO}_2\text{R}^{10}$ ,  $\text{NR}^{10}\text{C(O)SR}^{10}$ ,  $\text{NR}^{10}\text{SO}_2\text{R}^{10}$ ,  $\text{NR}^{10}\text{SO}_2\text{NR}^{10}\text{R}^{11}$ , nitro,  $\text{OR}^{10}$ ,  $\text{OCF}_3$ , aryloxy, heteroaryloxy,  $\text{SR}^{10}$ ,  $\text{S(O)R}^{10}$ ,  $\text{S(O)}_2\text{R}^{10}$ ,  $\text{SCF}_3$ ,  $\text{S(O)CF}_3$ ,  $\text{S(O)CF}_3$ ,  $\text{SO}_2\text{NR}^{10}\text{R}^{11}$ ,  $\text{SO}_3\text{R}^{10}$ ,  $\text{PO}_3\text{R}^{10}\text{R}^{11}$ , or halo, and on any position;

10  $\text{R}^{10}$ ,  $\text{R}^{11}$ , and  $\text{R}^{12}$  are independently selected from the group consisting of hydrogen,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkanoyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-10}$  cycloalkyl,  $\text{C}_{0-6}$  alkylaryl,  $\text{C}_{0-6}$  alkylheterocyclyl, and  $\text{C}_{0-6}$  alkylheteroaryl, or  $\text{R}^{10}$  and  $\text{R}^{11}$  taken together with the nitrogen to which they are attached complete a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $\text{C}_{1-6}$  alkyl or  $(\text{CH}_2)_{0-5}$  aryl; or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of formula (I).

2. A method according to claim 1 wherein  $\text{R}3$  is  $\text{H}$ .

20 3. A method according to claim 2 wherein  $\text{R}1$  is  $\text{H}$  or  $\text{CH}_3$ .

4. A method according to claim 2 wherein  $\text{Y}$  is selected from the group consisting of bisulfate, chloride, fumarate, iodide, maleate, methanesulfonate, nitrate, trifluoromethanesulfonate, and sulfate.

25 5. A method according to claim 4 wherein the compound is selected from the group consisting of:

2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide

30 5-Phenyl-2-ureido-thiophene-3-carboxylic acid amide

2-(3-Ethyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide

5-(3-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-Phenyl-2-ureido-thiophene-3-carboxylic acid methyl ester  
[5-Phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea  
5 2-(3-Methyl-ureido)-5-p-tolyl-thiophene-3-carboxylic acid amide  
5-(2-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(4-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
[5-(4-Fluoro-phenyl)-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea  
5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide  
10 5-(2-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Chloro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-p-Tolyl-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide  
5-Naphthalen-2-yl-2-ureido-thiophene-3-carboxylic acid amide  
15 1-Methyl-3-[5-phenyl-3-(1-ureido-methanoyl)-thiophen-2-yl]-urea  
5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide  
2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid methylamide  
5-(3-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Cyano-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
20 5-(4-Ethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Hydroxymethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Chloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
25 5-(3,4-Dichloro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Trifluoromethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Chloro-4-fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Methanesulfonyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
30 5-(3,4-Difluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Cyano-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(4-Dimethylamino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
35 5-(3-Fluoro-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(3-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-Benzo[1,3]dioxol-5-yl-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide

5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(3-Hydroxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-Methyl-5-(3-methyl-ureido)-[2,2]bithiophenyl-4-carboxylic acid amide  
5-(3-Acetyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid amide  
5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid methylamide  
2-(3-Methyl-ureido)-5-(3-trifluoromethyl-phenyl)-thiophene-3-carboxylic acid methylamide  
5-(4-Methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
10 5-(4-Hydroxy-3-methoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
5-(3,4-Dimethoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
15 5-Phenyl-2-ureido-thiophene-3-carboxylic acid phenylamide  
2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid phenylamide; and  
5-Phenyl-2-ureido-thiophene-3-carboxylic acid methylamide.

6. A method according to claim 4 wherein the compound is selected from the  
20 group consisting of:

2-(3-Methyl-ureido)-5-phenyl-thiophene-3-carboxylic acid amide  
5-Phenyl-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-Ureido-[2,3]bithiophenyl-4-carboxylic acid amide  
25 5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid amide  
5-(4-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid methylamide  
5-(3-Fluoro-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Ethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Methoxy-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
30 5-(3-Hydroxymethyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(4-Methanesulfonyl-phenyl)-2-ureido-thiophene-3-carboxylic acid amide  
5-(3-Methyl-ureido)-[2,3]bithiophenyl-4-carboxylic acid methylamide  
2-(3-Methyl-ureido)-5-(3-trifluoromethyl-phenyl)-thiophene-3-carboxylic acid methylamide  
35 5-(4-Amino-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide  
5-(4-Hydroxymethyl-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid

methylamide; and  
 5-(3,4-Dimethoxy-phenyl)-2-(3-methyl-ureido)-thiophene-3-carboxylic acid methylamide.

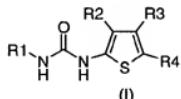
7. A method according to claim 1 wherein the kinase being inhibited is chk-1  
 5 kinase.

8. A method according to claim 1 wherein the present compounds are  
 administered as IKK $\beta$ /Chk1 kinase dual inhibitors for the treatment of cancer and  
 cancer-related diseases.

10 9. A method according to claim 1 wherein the disease or disorder being treated  
 is selected from the group consisting of leukemia, solid tumor cancer, metastases,  
 lymphomas, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer,  
 pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate  
 15 cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer,  
 head cancer and neck cancer, chronic inflammatory proliferative diseases, proliferative  
 cardiovascular diseases, proliferative ocular disorders and benign hyperproliferative  
 diseases.

20 10. A method according to claim 9 wherein the disease or disorder treated is  
 selected from the group consisting of psoriasis, rheumatoid arthritis, diabetic  
 retinopathy and hemangiomas.

11. A compound according to Formula (I) hereinbelow:



25

wherein:

R1 is selected from the group consisting of H, C<sub>1-2</sub> alkyl, XH, XCH<sub>3</sub>, C<sub>1-2</sub> alkyl-XH,  
 C<sub>1-2</sub> alkyl-XCH<sub>3</sub>, C(O)NH<sub>2</sub>, C(O)NHCH<sub>3</sub>, and C(O)-C<sub>1-2</sub> alkyl, provided that when  
 R1 is H, R2 is not CONH<sub>2</sub>, or provided that when R1 is C<sub>1-2</sub> alkyl, R2 is not

30 CONH<sub>2</sub>, with the preferred substitution being H or CH<sub>3</sub>;

X is selected from the group consisting of O, S, and NH;

R2 is selected from the group consisting of C(O)R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, C(O)NHR<sup>5</sup>,

C(O)NHC(=NH)R<sup>5</sup>, C(O)NHC(=NH)NR<sup>4</sup>R<sup>6</sup>, C(O)NHC(O)R<sup>5</sup>, C(O)NHC(O)NR<sup>5</sup>R<sup>6</sup>,

SO<sub>2</sub>R<sup>5</sup>, S(O)R<sup>5</sup>, SO<sub>2</sub>R<sup>5</sup>, and PO<sub>3</sub>R<sup>4</sup>R<sup>6</sup>;

5

R<sup>5</sup> and R<sup>6</sup> are, independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, and C<sub>6-6</sub> alkylheteroaryl, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms, optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl, such that any of the foregoing may be optionally substituted by one or more of group A and on any position;

15 R3 is H or halogen; with the preferred substitution being H;

R4 is aryl or heteroaryl optionally substituted by one or more of group A and on any position, provided that when R2 is CO<sub>2</sub>R<sup>5</sup> or CONH<sub>2</sub>, R4 is not phenyl, or provided that when R1 is H, R4 is not 4-pyridyl;

20

A is selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl, C(=NH)R<sup>7</sup>, COR<sup>7</sup>, CONR<sup>7</sup>R<sup>8</sup>, CON(O)R<sup>7</sup>R<sup>8</sup>, CONR<sup>7</sup>R<sup>8</sup>Y, CO<sub>2</sub>R<sup>7</sup>, C(O)SR<sup>7</sup>, C(S)R<sup>7</sup>, cyano, trifluoromethyl, NR<sup>7</sup>R<sup>8</sup>, N(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>COR<sup>7</sup>,

25 NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CON(O)R<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>CONR<sup>7</sup>R<sup>8</sup>Y, NR<sup>7</sup>CO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>C(O)SR<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>7</sup>SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, nitro, OR<sup>7</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>7</sup>, S(O)R<sup>7</sup>, S(O)<sub>2</sub>R<sup>7</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>7</sup>, PO<sub>3</sub>R<sup>7</sup>R<sup>8</sup>, and halo, wherein C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>6-6</sub> alkylaryl, C<sub>6-6</sub> alkylheterocycl, C<sub>6-6</sub> alkylheteroaryl, (CH<sub>2</sub>)<sub>0-6</sub>heteroaryl, aryloxy, and

30 heteroaryloxy may be optionally substituted by one or more of group D and on any position;

Y is an organic or inorganic anion;

D is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{6-6}$  alkylaryl,  $C_{6-6}$  alkylheterocyclyl,  $C_{6-6}$  alkylheteroaryl,  $C(=NH)R^7$ ,  $COR^7$ ,  $CONR^7R^8$ ,  $CON(O)R^7R^8$ ,  $CONR^7R^8Y$ ,  $COR^7$ ,  $C(O)SR^7$ ,

5  $C(S)R^7$ , cyano, trifluoromethyl,  $NR^7R^8$ ,  $N(O)R^7R^8$ ,  $NR^7R^8Y$ ,  $NR^7COR^7$ ,  $NR^7CONR^7R^8$ ,  $NR^7CONR^7R^8Y$ ,  $NR^7CO_2R^7$ ,  $NR^7C(O)SR^7$ ,  $NR^7SO_2R^7$ ,  $NR^7SO_2NR^7R^8$ , nitro,  $OR^7$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^7$ ,  $S(O)R^7$ ,  $S(O)_2R^7$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^7R^8$ ,  $SO_3R^7$ ,  $PO_3R^7R^8$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{6-6}$  alkylaryl,

10  $C_{6-6}$  alkylheterocyclyl,  $C_{6-6}$  alkylheteroaryl,  $(CH_2)_{6-6}$  heteroaryl, aryloxy, and heteroaryloxy may be optionally substituted by one or more of group E and on any position;

$R^7$ ,  $R^8$ , and  $R^9$  are independently selected from the group consisting of hydrogen,  $C_{1-10}$

15 alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{6-6}$  alkylaryl,  $C_{6-6}$  alkylheterocyclyl, and  $C_{6-6}$  alkylheteroaryl, or  $R^7$  and  $R^8$  taken together with the nitrogen to which they are attached may optionally form a ring having 3 to 7 carbon atoms optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen, or nitrogen, substituted with hydrogen,  $C_{1-6}$  alkyl or  $(CH_2)_{6-3}$  aryl, wherein any

20 of the foregoing may be substituted by one or more of group E and on any position;

E is selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{6-6}$  alkylaryl,  $C_{6-6}$  alkylheterocyclyl,  $C_{6-6}$  alkylheteroaryl,  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,  $CON(O)R^{10}R^{11}$ ,  $CONR^{10}R^{11}R^{12}Y$ ,  $COR^{10}$ ,  $C(O)SR^{10}$ ,

25  $C(S)R^{10}$ , cyano, trifluoromethyl,  $NR^{10}R^{11}$ ,  $N(O)R^{10}R^{11}$ ,  $NR^{10}R^{11}R^{12}Y$ ,  $NR^{10}COR^{10}$ ,  $NR^{10}CONR^{10}R^{11}$ ,  $NR^{10}CON(O)R^{10}R^{11}$ ,  $NR^{10}CONR^{10}R^{11}R^{12}Y$ ,  $NR^{10}CO_2R^{10}$ ,  $NR^{10}C(O)SR^{10}$ ,  $NR^{10}SO_2R^{10}$ ,  $NR^{10}SO_2NR^{10}R^{11}$ , nitro,  $OR^{10}$ ,  $OCF_3$ , aryloxy, heteroaryloxy,  $SR^{10}$ ,  $S(O)R^{10}$ ,  $SCF_3$ ,  $S(O)CF_3$ ,  $S(O)_2CF_3$ ,  $SO_2NR^{10}R^{11}$ ,  $SO_3R^{10}$ ,  $PO_3R^{10}R^{11}$ , and halo, wherein  $C_{1-10}$  alkyl,  $C_{1-10}$  alkanoyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{3-10}$  cycloalkyl,  $C_{6-6}$  alkylaryl,  $C_{6-6}$  alkylheterocyclyl,  $C_{6-6}$  alkylheteroaryl

30 may be substituted by one or more of  $C(=NH)R^{10}$ ,  $COR^{10}$ ,  $CONR^{10}R^{11}$ ,

CON(O)R<sup>10</sup>R<sup>11</sup>, CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, CO<sub>2</sub>R<sup>10</sup>, C(O)SR<sup>10</sup>, C(S)R<sup>10</sup>, cyano, trifluoromethyl, NR<sup>10</sup>R<sup>11</sup>, N(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>COR<sup>10</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CON(O)R<sup>10</sup>R<sup>11</sup>, NR<sup>10</sup>CONR<sup>10</sup>R<sup>11</sup>R<sup>12</sup>Y, NR<sup>10</sup>CO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>C(O)SR<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>10</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>,  
5 nitro, OR<sup>10</sup>, OCF<sub>3</sub>, aryloxy, heteroaryloxy, SR<sup>10</sup>, S(O)R<sup>10</sup>, S(O)<sub>2</sub>R<sup>10</sup>, SCF<sub>3</sub>, S(O)CF<sub>3</sub>, S(O)<sub>2</sub>CF<sub>3</sub>, SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, SO<sub>3</sub>R<sup>10</sup>, PO<sub>3</sub>R<sup>10</sup>R<sup>11</sup>, or halo, and on any position;

R<sup>10</sup>, R<sup>11</sup>, and R<sup>12</sup> are independently, selected from the group consisting of hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkanoyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> cycloalkyl, C<sub>9-6</sub> alkylaryl, C<sub>9-6</sub> alkylheterocyclyl, and C<sub>9-6</sub> alkylheteroaryl, or R<sup>10</sup> and R<sup>11</sup> taken together with the  
10 nitrogen to which they are attached complete a ring having 3 to 7 carbon atoms  
optionally containing 1, 2, or 3 heteroatoms selected from nitrogen, sulfur, oxygen,  
or nitrogen, substituted with hydrogen, C<sub>1-6</sub> alkyl or (CH<sub>2</sub>)<sub>0-3</sub>aryl;  
or a pharmaceutically acceptable inorganic or organic salt, esters, or other prodrug of  
formula (I).

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/31752

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 333/36; A61K 31/38

US CL : 549/69; 514/447

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 549/69; 514/447

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 6,344,476 B1 (RANGES et al) 05 February 2002 (05.02.2002), columns 5-8.	1-11
A, P	US 6,414,013 B1 (FANCELLI et al) 02 July 2002 (02.07.2002), columns 2-4.	1-11
A, E	US 6,476,023 B1 (CIRILLO et al) 05 November 2002 (05.11.2002), columns 6-8.	1-11

 Further documents are listed in the continuation of Box C. See patent family annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier application or patent published on or after the international filing date
- \*L\* documents which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* documents referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\*

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\*

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\*

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*&amp;\*

document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

02 December 2002 (02.12.2002)

18 DEC 2002

Name and mailing address of the ISA/US

U.S. Patent and Trademark Office  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Deborah C Lambkin

Telephone No. 703-308-1235